PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/135, 31/405

A1

(11) International Publication Number: WO 98/18458

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/US97/15542

(22) International Filing Date: 4 September 1997 (04.09.97)

(30) Priority Data:
60/028,790 31 October 1996 (31.10.96) US

(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134–2099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DeSANTIS, Louis, Jr. [US/US]; 2316 Winton Terrace West, Fort Worth, TX 76109 (US). OSBORNE, Neville [GB/GB]; 12 Mill Street, Myrtlehouse, Eynshan, Oxford OX8 1JS (GB). SHARIF, Najam [GB/US]; 7 Courtney Court, Arlington, TX 76015 (US). SALLEE, Verney [US/US]; 304 Diamond Lane, Burleson, TX 76028 (US).

(74) Agents: YEAGER, Sally, S.; Alcon Laboratories, Inc., Patent Dept., Q–148, 6201 South Freeway, Fort Worth, TX 76134–2099 (US) et al.

(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: OPTHALMOLOGICAL COMPOSITIONS CONTAINING SEROTONIN 5–HT1A RECEPTOR AGONIST AND THEIR USE IN THE TREATMENT OF GLAUCOMA

(57) Abstract

Methods and compositions for controlling intraocular pressure with 5–HT_{1A} receptor agonists that inhibit adenylyl cyclase are disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

OPTHALMOLOGICAL COMPOSITIONS CONTAINING SEROTONIN 5-HT1A RECEPTOR AGONIST AND THEIR USE IN THE TREATMENT OF GLAUCOMA

The present invention relates to the use of compounds that activate the 5-HT_{1A} subtype of serotonin receptor and inhibit adenylyl cyclase activity in the eye to lower intraocular pressure and treat glaucoma and ocular hypertension.

Background of the Invention

Serotonin (5-hydroxytryptamine or 5-HT) is a natural neurotransmitter that acts on a family of serotonin receptors located in various tissues throughout the body, including the eye (Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., Humphrey, P.A., "VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)," *Pharmacological Reviews*, 46(2):157-203 (1994)). Serotonin receptors include a family of receptor subtypes linked through their amino acid sequence homology and coupled to characteristic cellular responses through second messengers, cyclic adenosine monophosphate (cAMP), and inositol triphosphate (IP3) (Zifa, E., Fillion, G.; "5-Hydroxytryptamine Receptors", *Pharmacological Reviews*, 44(3):401-440 (1992)). The 5-HT_{1A} receptor subtype can be negatively coupled to adenylyl cyclase, the enzyme that synthesizes cAMP, so that its activation by a 5-HT_{1A} agonist results in the inhibition of cAMP synthesis (Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., Humphrey, P.A., "VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)," *Pharmacological Reviews*, 46(2):157-203 (1994) and Zifa, E., Fillion, G.; "5-Hydroxytryptamine Receptors", *Pharmacological Reviews*, 44(3):401-440 (1992)).

Serotonin binding sites have been found in membrane preparations obtained from rabbit ciliary processes, the ocular tissue involved in aqueous humor secretion (Mallorga, P., Sugrue, M.F., "Characterization of serotonin receptors in the iris + ciliary body of the albino rabbit," *Current Eye Research*, 6(3):527-532 (1987) and Chidlow, G., DeSantis, L.M., Sharif, N.A., Osborne, N.N., "Characteristics of [^{3}H]5-Hydroxytryptamine Binding to Iris-Ciliary Body Tissue of the Rabbit" *Investigative Ophthalmology & Visual Science*, 36(11):2238-2245 (1995)). Competitive binding inhibition experiments using various ligands, with known or putative serotonin receptor subtype selectivity, were performed and the results indicated that the nature of one of the serotonin binding sites, i.e., receptors, located in rabbit ciliary processes is that of the 5-HT_{1A} subtype (Mallorga, P., Sugrue, M.F., "Characterization of serotonin receptors in the iris + ciliary body of the albino rabbit," *Current Eye Research*, 6(3):527-532 (1987) and Chidlow, G., DeSantis, L.M., Sharif, N.A., Osborne, N.N., "Characteristics of [^{3}H]5-Hydroxytryptamine Binding to Iris-Ciliary Body Tissue of the Rabbit" *Investigative Ophthalmology & Visual Science*, 36(11):2238-2245 (1995)). Thus, a population of 5-HT_{1A} receptors is present in rabbit ciliary processes and are negatively coupled to adenylyl cyclase (Barnett, N.L., Osborne, N.N., "The Presence of Serotonin (5-HT_1) Receptors Negatively Coupled to Adenylate Cyclase in Rabbit and Human Iris-Ciliary Processes", *Exp. Eye Res.*, 57:209-216 (1993) and Tobin, A.B., Osborne, N.N., "Evidence for the Presence of Serotonin Receptors Negatively Coupled to Adenylate Cyclase in the Rabbit Iris-Ciliary Body," *Journal of Neurochemistry*, 686-690 (1989)).

The question of the physiological relevance of these receptors can be raised. To this end, experiments have been performed to investigate the effect of ocularly applied serotonin on the intraocular pressure(IOP) of the rabbit eye (Meyer-Bothling, U., Bron, A.J., Osborne, N.N.; "Topical Application of Serotonin or the 5-HT_1-Agonist 5-CT Intraocular Pressure in Rabbits," *Investigative Ophthalmology & Visual Science*, 34(10):3035-3042 (1993) and Krootila, K., Palkama, A., Uusitalo, H.; "Effect of Serotonin and Its Antagonist (Ketanserin) on Intraocular Pressure in the Rabbit," *Journal of Ocular Pharmacology*, 3(4):279-290 (1987)). It has been reported that serotonin raised the IOP of

the rabbit, leading one to believe that the activation of 5-HT_{1A} receptors in rabbit ciliary processes stimulates the secretion of aqueous humor and increases the IOP (Meyer-Bothling, U., Bron, A.J., Osborne, N.N.; "Topical Application of Serotonin or the 5-HT_1-Agonist 5-CT Intraocular Pressure in Rabbits," *Investigative Ophthalmology & Visual Science*, 34(10):3035-3042 (1993)). However, the fact that serotonin acts on all subtypes of serotonin receptors makes the interpretation more difficult as it also lowered IOP in the rabbit according to another report (Krootila, K., Palkama, A., Uusitalo, H.; "Effect of Serotonin and Its Antagonist (Ketanserin) on Intraocular Pressure in the Rabbit," *Journal of Ocular Pharmacology*, 3(4):279-290 (1987)).

Additionally, it has been reported that 5-HT_2 receptors exist in the rabbit iris-ciliary body (which includes the ciliary processes) (Chidlow, G., DeSantis, L.M., Sharif, N.A., Osborne, N.N., "Characteristics of [^{3}H]5-Hydroxytryptamine Binding to Iris-Ciliary Body Tissue of the Rabbit" *Investigative Ophthalmology & Visual Science*, 36(11):2238-2245 (1995)). An antagonist of these receptors, ketanserin, has been shown to produce lowering of IOP; however, ketanserin also has affinity for alpha adrenergic receptors which could also be responsible for the IOP lowering effect (Chang, F.W., Burke, J.A., Potter, D.E., "Mechanism of the Ocular Hypotensive Action of Ketanserin," *Journal of Ocular Pharmacology*, 1(2):137-147 (1985) and Costagliola, C., Scibelli, G., Fasano, M.L., Ferrara, L.A., Mastropasqua, L.; "Effect of Oral Ketanserin Administration on Intraocular Pressure in Glaucomatous Patients," *Exp. Eye Res.*, 52:507-510 (1991)). Thus, it is not clear whether 5-HT_2 serotonin receptors play a major role in mediating the effect of ketanserin on IOP.

Using the techniques of molecular biology, it has been shown that rabbit ciliary processes contain the message for the 5-HT_7 subtype serotonin receptor (Chidlow, G., DeSantis, L.M., Sharif, N.A., Osborne, N.N., "Characteristics of [^{3}H]5-Hydroxytryptamine Binding to Iris-Ciliary Body Tissue of the Rabbit" *Investigative Ophthalmology & Visual Science*, 36(11):2238-2245 (1995) and Osborne, N.N., Chidlow, G., "Do Beta-Adrenoceptors and Serotonin 5-HT_{1A} Receptors Have Similar Functions in the Control of Intraocular Pressure in the Rabbit?" *Ophthalmologica*, 210:308-314

(1996)). However, no function in this tissue has yet been ascribed to this receptor. In brain tissue, this receptor is positively coupled to adenylyl cyclase so its function in the ciliary process would appear to be diametrically opposed to that of the 5-HT_{1A} receptor (Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., Humphrey, P.A., "VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)," *Pharmacological Reviews*, 46(2):157-203 (1994)). Moreover, 5-HT_{1A} -like receptors that are positively coupled to adenylyl cyclase have also been reported (Zifa, E., Fillion, G.; "5-Hydroxytryptamine Receptors", *Pharmacological Reviews*, 44(3):401-440 (1992)).

Summary of the Invention

It has now been unexpectedly discovered that compounds which act on the 5-HT_{1A} subtype of serotonin receptors to inhibit adenylyl cyclase activity produce a lowering of intraocular pressure in mammalian species when applied topically to the eye. This pharmacological effect is useful to treat the conditions of glaucoma and ocular hypertension.

Description of Preferred Embodiments

It is believed that the net result from the stimulation of the multiple serotonin receptors in the ciliary processes of the eye depends on the relative importance of each receptor for regulating the physiological process of aqueous humor secretion and that the 5-HT_{1A} receptor plays the dominant role for determining the direction of this effect and whether aqueous humor secretion is increased or decreased. Thus, the pharmacological activation of the serotonin receptor subtype, 5-HT_{1A}, that is negatively coupled to adenylyl cyclase tissue, results in a lowering of IOP and thus are useful to treat glaucoma and ocular hypertension.

Two compounds, 8-hydroxy dipropylamino tetraline (DPAT) and 5-methoxy-N,N-dimethyltryptamine, that have a relatively high affinity for serotonin binding sites of rabbit ciliary processes, were studied for their effect on IOP. When applied to normotensive rabbit eyes, 8-hydroxy-DPAT was found to produce a decrease of IOP. Additionally, 5-methoxy-N,N-dimethyl tryptamine produced a decrease of IOP when applied topically to the (ocular) hypertensive monkey eye.

The compounds listed in Table 2 of Zifa, E., Fillion, G.; "5-Hydroxytryptamine Receptors", *Pharmacological Reviews*, 44(3):401-440 (1992), which is incorporated herein by reference, can be used according to the present invention. Compounds which are full agonists (compounds which can completely activate the receptor to produce a maximal response) at 5-HT_{1A} receptors are most preferred; partial agonists (compounds which produce a submaximal response when receptors are fully activated) being less preferred. Full agonists (to the extent known) can be selected from, but not limited to, the following compounds: R(+) 8-hydroxy (DPAT); buspirone; N,N-dipropyl-5-carboxamidotryptamine; and 5-methoxy-N,N-dimethyltryptamine. Partial agonists at 5-HT_{1A} receptors include, but are not limited to, S(-)-8-hydroxy DPAT and spiroxatrine.

The preferred route of administration is topically to the affected eye. The dosage range for topical administration is generally between about 0.3 and about 3000 micrograms per eye (μg/eye) and is preferably between about 1 and about 1000 μg/eye and most preferably between 30 and 300 μg/eye. The compounds of the present invention can be administered as solutions, suspensions, gels, solid inserts, or emulsions (dispersions) in a suitable vehicle.

The compounds can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving the compound in a

physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Furthermore, the ophthalmic solution may contain a thickener such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

In forming compositions for topical administration, the compounds of the present invention are generally formulated at a concentration of about 0.001 to about 10 weight/volume % in an aqueous solution at a pH between about 4.5 and about 8.0. The compounds are preferably formulated at concentrations of about 0.0033 to 3.33% and, most preferably, at concentrations of about 0.1 to 1%. While the precise regimen is left to the discretion of the clinician, it is recommended that the compositions be topically applied by placing one or more drops in each eye one or more times per day.

We Claim:

1. A method for controlling intraocular pressure, which comprises, administering topically to the eye of a person suffering from glaucoma or ocular hypertension a composition comprising a therapeutically effective amount of a 5-HT_{1A} receptor agonist that inhibits adenylyl cyclase.

2. The method of Claim 1 wherein the 5-HT_{1A} receptor agonist is selected from the group consisting of R(+) 8-hydroxy dipropylamino tetraline and 5-methoxy-N,N-dimethyltryptamine.

3. The method of Claim 2 wherein the 5-HT_{1A} receptor agonist is R(+) 8-hydroxy dipropylamino tetraline.

4. A topical, ophthalmic composition for controlling intraocular pressure, comprising a therapeutically effective amount of a 5-HT_{1A} receptor agonist that inhibits adenylyl cyclase.

5. The composition of Claim 4 wherein the 5-HT_{1A} receptor agonist is selected from the group consisting of R(+) 8-hydroxy dipropylamino tetraline and 5-methoxy-N,N-dimethyltryptamine.

6. The composition of Claim 5 wherein the 5-HT_{1A} receptor agonist is R(+) 8-hydroxy dipropylamino tetraline.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 97/15542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135 A61K31/405

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHIDLOW ET AL: "The ocular blood flow tonograph: A new instrument for the measurement of intraocular pressure in rabbits" EXP. EYE RES., vol. 63, no. 4, 1996, pages 463-69, XP002051580 * p.468, left hand col., 1st full par. * --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 1998	30. 01. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 97/15542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OSBORNE ET AL: "Do beta-adrenoceptors and serotonin 5-HT1A receptors have similar functions in the control of intraocular pressure in the rabbit?" OPHTHAMOLOGICA, vol. 210, 1996, pages 308-14, XP002051581 cited in the application * Abstract; p.312, left hand col., 3rd par.; Fig.4; p.312, right hand col., bottom-p.313, bottom *	1-6
X	US 5 229 387 A (CLARK ROBIN D ET AL) 20 July 1993 * col.1, l.41; col.21, l.2-11; claim 27 *	1,2,4
X	US 5 196 434 A (TAVERNE THIERRY ET AL) 23 March 1993 * col.5, l.67; col.6, l.14; claims 10 and 11 *	1,4
X	MANO T ET AL: "THE EFFECT OF MKC-242, DELECTIVE 5-HT1A AGONIST ON INTRAOCULAR PRESSURE IN RABBITS" INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 37, no. 3, 21 April 1996, page 1103 XP000672609 see the whole document	1-6
P,X	EP 0 771 563 A (MITSUBISHI CHEM CORP) 7 May 1997 * claims 1-5 and 8 *	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/US 97/15542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5229387 A	20-07-93	NONE	
US 5196434 A	23-03-93	FR 2667068 A	27-03-92
		AT 160344 T	15-12-97
		AU 644212 B	02-12-93
		AU 8471191 A	16-04-92
		CA 2052234 A	27-03-92
		DE 69128231 D	02-01-98
		EP 0478446 A	01-04-92
		JP 2053210 C	10-05-96
		JP 6100548 A	12-04-94
		JP 7086097 B	20-09-95
		NZ 239929 A	22-12-94
		US 5225409 A	06-07-93
		US 5234924 A	10-08-93
		US 5268381 A	07-12-93
		US 5296477 A	22-03-94
EP 0771563 A	07-05-97	NONE	